Inflammatory diseases of the parathyroid gland

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Date of submission 13 May 2011

Accepted for publication 14 July 2011

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(2011) *Histopathology* 59, 897–908

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Aims: Inflammatory disorders of the parathyroid gland are very rare as compared with those of other endocrine organs. The aim of this study was to provide the first systematic review of this condition.

Methods and results: A 42-year-old patient underwent surgery for recurrent secondary hyperparathyroidism. Histology showed hyperplastic parathyroiditis defined by a mixed inflammatory infiltrate with active germinal centres. Molecular markers revealed significant upregulation of CD68 in an ischaemic background (hypoxia-inducible factor 1 upregulation) with mitochondrial reaction (malate dehydrogenase 2 upregulation) and hyperparathyroidism (carbonic anhydrase 4 upregulation). Our case demonstrates true intrapathyroid inflammation with terminal B-cell differentiation. We searched PubMed, ISI Thompson and Google Scholar up to January 2011, using the terms 'parathyroiditis',

'inflammation of parathyroid gland', 'lymphocytic infiltrate', 'tuberculosis of the parathyroid', 'sarcoidosis', and 'granulomatous inflammation'. Three autopsy series, 27 articles and 96 case reports with inflammatory parathyroid disorders were identified. Autopsy series showed lymphocytic infiltrates in up to 16% of all cases. The entire material reported lymphocytic infiltrates ($n = 69$), parathyroiditis with germinal centres ($n = 15$), sarcoidosis ($n = 6$), tuberculosis ($n = 4$), and other granulomatous diseases ($n = 2$).

Conclusions: Distinct inflammatory and granulomatous processes in the parathyroid gland are rare. Scanty lymphocytic infiltrates are common, and occur in generalized inflammatory conditions or venous congestion. We note the surprising absence of an association between histological proof of parathyroiditis and hypoparathyroidism.

Keywords: inflammation, lymphocytic infiltrate, parathyroid gland, parathyroiditis, primary hyperparathyroidism

Abbreviations: CA4, carbonic anhydrase 4; CT, computed tomography; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HIF1A, hypoxia-inducible factor 1A; M6PR, mannose 6-phosphate receptor; MDH2, malate dehydrogenase 2; MGB, minor groove binder; PCR, polymerase chain reaction; PTH, parathyroid hormone; RT, reverse transcription

Introduction

Inflammatory disorders of the parathyroid gland are rare as compared with those of other endocrine organs.^{1–4} These entities are poorly defined, and descriptive terms such as lymphocytic infiltrate, parathyroiditis and lymphocytic parathyroiditis are used, resulting in no agreed scheme of classification.

Inflammation in other endocrine organs such as the thyroid has a long list of notable clinical associations. Thyroiditis, for example, is known to be associated with hypothyroidism, goitres, thyrotoxicosis, and hashitoxicosis,^{5,6} but no such clinical associations have been defined for parathyroid inflammatory disorders. Thyroiditis is associated with severe disturbances in thyroid function, with inflammatory effects ranging from thyrotoxicosis resulting from hormone releasing thyroiditis to chronic subclinical and clinical hypothyroidism, when the gland is transformed into a scar. With regard to parathyroid inflammation, very little is known about its effects on parathyroid function. A

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number of studies have demonstrated autoimmune hypoparathyroidism; however, none has shown histological evidence of inflammatory processes within the parathyroids as is seen in parathyroiditis.^{7–9}

Because of this terminological variation and the paucity of recent studies, it is not generally clear how to classify inflammatory parathyroid entities. It is also not clear whether such descriptive nosological entities relate to specific clinical constellations. This article is aimed at clarifying the pathological presentations and their clinical associations by using findings from an index patient with hyperplastic parathyroiditis; the molecular markers of this lesion are compared with a set of normal parathyroid glands, hyperplasias, and adenomas. We have therefore attempted to improve our understanding of these rare conditions by a review of the literature. It also makes minor contributions to our understanding of functional aspects of inflammatory parathyroid disease.

Materials and methods

A systematic search was conducted of the published literature on inflammatory diseases of the parathyroid gland. The databases searched included PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), Thompson ISI (<http://apps.isiknowledge.com/>) and Google Scholar; the search terms used were 'parathyroiditis', 'inflammation of parathyroid gland', 'lymphocytic infiltrate', 'tuberculosis', 'sarcoidosis', and 'granulomatous inflammation'. A hand search of article bibliographies was also performed with the ISI Thompson Web of Knowledge Citation report, enabling further articles to be retrieved. From the initial electronic search of 185 articles for possible inclusion, 27 articles were retained following title and abstract reviews; these articles reported on a total of 96 patients with inflammatory diseases of the parathyroid gland, including parathyroiditis ($n = 15$), lymphocytic infiltrate ($n = 69$), sarcoidosis of the parathyroid gland ($n = 6$), tuberculosis ($n = 14$), and granulomatous disease ($n = 2$).^{10–36} The inclusion criterion was unambiguous evidence of inflammatory processes of the parathyroid gland in the form of a histological description.

Histopathological descriptions were evaluated from the author's summary diagnosis and by analysing the information provided by the authors regarding the presence of lymphocytic infiltrate, parathyroiditis, and granulomatous inflammation. The terminology for parathyroiditis was inconsistent. After review of all histological descriptions, we found two fundamentally different patterns, and grouped patients according to these descriptions:

1. The non-specific pattern is marked by diffuse lymphocytic infiltrates in the direct vicinity of venules without evidence of lymphocyte maturation or immune-mediated tissue damage, such as fibrosis or epithelial degeneration.
2. The pattern of lymphocytic parathyroiditis is characterized by interstitial lymphocytes away from the vessels with terminal differentiation (plasma cells) and/or formation of germinal centres.

Data were extracted by one researcher and checked by another with standardized extraction tables developed *a priori*. Data were pooled as individual cases in a single contingent SPSS table.

PATIENT

This 42-year-old male Caucasian patient suffered from end-stage renal failure resulting from hyperplastic kidney that he had suffered from since 1995, when he was put on continuous ambulatory peritoneal dialysis. He developed severe secondary hyperparathyroidism with fatigue and bone pain, failed on calcimimetics, and underwent a total cervical parathyroidectomy with central lymph node clearance and thymectomy in 2007. Histopathology demonstrated four parathyroid glands with nodular hyperplasia, weighing 4.96 g, 1.64 g, 1.23 g, and 0.71 g. Two lymph nodes showed only reactive changes; the thymus and mediastinal fat resection weighed 125.5 g, and were histologically normal. Postoperatively, the parathyroid hormone (PTH) level dropped to 97 ng/l (normal 13–75 ng/l) in the presence of a low normal corrected calcium level of 2.29 mm and a normal phosphate level (Figure 1). The presence of PTH at this point was explained by the 60-mg parathyroid autotransplant into the forearm extensor muscles. An increase in the PTH level to >10-fold upper normal levels, with recurrent fatigue and bone aches, led to excision of the autotransplant from the left forearm after negative imaging findings in the neck and chest. This revealed 1.99 g of nodular parathyroid hyperplasia. The postoperative PTH levels dropped to 52 ng/l, in the presence of a normal corrected calcium level supported by high-dose active vitamin D treatment. Over the subsequent 2 years, the patient showed extreme fluctuations of PTH levels between the upper normal limit of 70 ng/l and 2000 ng/l with concordant fluctuations in symptomatology. Complex re-imaging with ultrasound and magnetic resonance imaging of the neck, contrast computed tomography (CT) of the neck and chest and fusion imaging including Technetium Tc 99m sestamibi single-photon emission computed tomography (MIBI-SPECT) sug-

Figure 1. The clinical course of our case with parathyroiditis. Parathyroid hormone (PTH) levels are expressed as times the upper normal limit of the methods used, as two different assays were used to obtain PTH measurements for this patient. Calcium normal (2.15–2.60 mm); phosphate normal (0.80–1.40 mm).

gested a 1-cm lesion riding the aortic arch. In July 2010, initial thoracoscopic exploration showed this to be a probable tuberculous lymph node, and surgery was therefore changed to thoracotomy with exploration of the aortopulmonary window. The surgery was followed by normalization of the PTH and calcium levels. The specimen measured 35 × 19 × 21 mm and weighed 6 g. It showed a nodular growth pattern composed of oncocyctic and clear cell islands. The stroma was expanded by a prominent diffuse and patchy mixed inflammatory infiltrate, comprising mainly plasma cells and lymphocytes. There was interstitial haemorrhage, congestion, and large numbers of haemosiderin-laden macrophages. There was no vascular invasion, confluent necrosis, or undue mitotic activity. The features were consistent with hyperplastic parathyroiditis (Figures 2 and 3).

TARGETED GENE EXPRESSION ANALYSIS

Total RNA was isolated from control parathyroid glands ($n = 5$, from thyroidectomies with no parathyroid pathology), hyperplasias ($n = 10$), and adenomas ($n = 10$), by the use of commercial kits (RNeasy kit;

Figure 2. Parathyroid tissue reveals thick trabeculae of chief cells dissected by inflamed stroma with dilated blood vessels and haemosiderin-laden macrophages (haematoxylin and eosin, ×40).

Qiagen, Crawley, UK), following the manufacturer's instructions. After extraction, the RNA was treated with DNaseI (DNA-free; Ambion, Austin, TX, USA) at 37°C for 20 min in a 50-µl reaction containing total RNA in water, 5 µl of DNA-free buffer, 2 µl of Suprase

Figure 3. Chronic parathyroiditis reveals interstitial chronic inflammation with focal degenerative changes [fat infiltration, A, haematoxylin and eosin (H&E), $\times 100$] as indicated by tissue damage, cell infiltrate containing mature plasma cells (antigen-driven terminally differentiated B cells, B, H&E, $\times 200$), and increased vascular permeability with red blood cell extravasation, both recent (C, H&E, $\times 200$) and chronic (siderophages, D, H&E, $\times 400$).

RNase inhibitor (Ambion), and 1 μ l of DNaseI. To clean up the RNA, the mixture was loaded onto an RNeasy column and total RNA was eluted with water in a volume of 40 μ l. The quantity and quality of the RNA samples were determined with the RNA 6000 LabChip kit (Agilent Technologies, Wilmington, DE, USA).

Reverse transcription

Reverse transcription (RT) was carried out in a 20- μ l reaction volume containing 1 $\times$ PCR buffer II (PE Biosystems, Foster City, CA, USA), 25 units of Moloney murine leukaemia virus reverse transcriptase (SuperScript II; Life Technologies, Carlsbad, CA, USA), 8 units of RNase inhibitor (PE Biosystems), 7.5 mM $MgCl_2$, 1.0 mM each 2-deoxynucleotide 5'-triphosphate (Roche Molecular Biochemicals, Indianapolis, IN, USA), 2.5 μ M

random hexamers (PE Biosystems), and 30 ng of total RNA. RT was performed by incubating the samples at 25°C for 10 min, 48°C for 40 min and 95°C for 5 min in a PerkinElmer GeneAmp PCR System 9700. No-RT controls were carried out in all cases by using the same RT reaction mixture but substituting diethylpyrocarbonate- H_2O for the reverse transcriptase. For all quantitative analyses, two RT reactions were carried out for each RNA sample by using 200 and 50 ng per 100 μ l of RT reaction mixture. The no-RT controls were carried out with 200 ng of RNA.

Real-time quantitative polymerase chain reaction (PCR)

Quantitative real-time PCR is based on the detection of a fluorescent signal that increases linearly with accumulating amplification product during the PCR reaction. During the extension phase of PCR, the probe is

cleaved by the endogenous 5'-nuclease activity of *AmpliTaq* Gold polymerase, which cleaves the reporter chromophore from the TaqMan probe, leading to an increase in the intensity of reporter fluorescence. The increase in fluorescence (ΔR_n) signal is continuously measured and plotted versus PCR cycle number, reflecting the amount of PCR amplification product. The ABI PRISM 7700 detection system software (Applied Biosystems, Foster City, CA, USA) calculates ΔR_n by subtracting the fluorescence signal of the baseline emission during cycles 3–6 from the fluorescence signal of the product at any given time. A threshold was set at the early log phase of product accumulation. The threshold cycle number value (C_T) is the cycle number at which each sample's amplification plot reaches this threshold. We carried out real-time PCR with TaqMan unlabeled PCR primers and 6-carboxyfluorescein dye-labelled TaqMan minor groove binder (MGB; 6-carboxytetramethylrhodamine) primer probes on an ABI PRISM 7700 Sequence Detection System (Applied Biosystems). The MGB probes have an MGB at the 3'-end of the probe, which increases the T_m of probes, allowing the use of shorter probes. PCR primers and fluorogenic probes (TaqMan) were designed by using PRIMER EXPRESS software (PE Biosystems). All primer sequences are given in Table 1. Wherever possible, primers and probes were designed to span introns in the genomic DNA, thereby minimizing the potential for confounding of the signal by contaminating genomic DNA. TaqMan primers and MGB probes for target genes (Table 1) were obtained from Assays on Demand (Applied Biosystems). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) TaqMan primers and MGB probes were obtained as pre-developed assay reagents from Applied Biosystems. PCR reactions were performed in 25- μ l volumes consisting of 1 $\times$ PCR buffer A (PE Biosystems), 3.5 mM $MgCl_2$, 300 μ M each dATP, dCTP, dGTP, and dTTP, 1.25 units of *AmpliTaq* Gold (PE Biosystems),

and 2.5 μ l of the appropriate RT reaction product. The primers were present at 300 nM, and the TaqMan probe was present at 200 nM. The GAPDH amplification primers were each present at 100 nM, and the TaqMan probe was present at 100 nM. Amplification and detection were carried out by using an ABI 7700 detection system as follows: one cycle at 95°C for 12 min, 40 cycles at 95°C for 15 s, and 60°C for 1 min. All cases were conducted with duplicate samples and C_T units obtained as the average of the results from the replicates. C_T is defined as the threshold cycle for PCR amplification that is detected by the ABI PRISM DNA sequence detector at a threshold value set at 0.45 for each run. The calculated C_T values were analysed in Microsoft Excel.

Calculation of relative expression

Relative mRNA expression of target genes was calculated with the comparative C_T method. The amount of target gene was normalized to the endogenous *GAPDH* control gene to control for quantity of RNA input. The difference in C_T values was calculated for each mRNA by taking the mean C_T of duplicate reactions and subtracting the mean C_T of duplicate reactions for reference RNA measured on an aliquot from the same RT reaction: $\Delta C_T = C_T(\text{target gene}) - C_T(\text{GAPDH})$. A logarithmic transformation was used to graphically tabulate the data.

Results

There were two large autopsy studies specifically addressing the issue of parathyroiditis, one comprising 225 patients¹⁰ and one containing 589 patients,³⁶ in whom 1637 parathyroid glands were dissected. Both studies were based on unselected autopsy cohorts, with male patients accounting for 51.1% and 57.0%, respectively. Seemann's study revealed two patients

Table 1. Primer sequences

Gene	Forward primer (5'–3')	Reverse primer (5'–3')
CA4	TCGGAGCACAGCCTCGAT	CTCGATGTCCCCTTCTCTTCTC
M6PR	GCAGAAGCTGGGTGTCATAGG	CACGGAGGATGCGGTCTTAT
CD68	GAGGCCTGGGGCATCTCTGTA	CGAGTTGCTGCAACTGAAGCT
MDH2	CCGCCTGACCCTCTATGATATCC	TCCGGCTTAGCCTTGACCAC
HIF1A	TACTGGGGTTCATGATGATTATTGTGG	ACTTCAGGAACCGGCGTGATTATTA

CA4, Carbonic anhydrase 4; HIF1A, hypoxia-inducible factor 1A; M6PR, mannose 6-phosphate receptor; MDH2, malate dehydrogenase 2.

with secondary hyperparathyroidism, no patient with known primary hyperparathyroidism, and no patient with clinical hypoparathyroidism. Seemann described lymphocytic infiltrates, perivenular in distribution, in 38 cases (16.9%). Only seven of the cases showed interstitial infiltrates. Fifteen cases showed only isolated and small accumulation of lymphoid cells, 18 cases showed larger groups of cells, and only five cases showed several large cell clusters. In only one case did the lymphocytic infiltrate involve all four glands (the patient died from myocardial infarction). The infiltrate was predominantly lymphocytic in 27 cases, lymphoplasmacytic in four cases, predominantly plasmacytic in three cases, and mixed (plasma cells, lymphocytes, and histocytes) in four cases. The underlying conditions comprised severe systemic inflammation such as septicaemia, pneumonia, purulent meningitis, pyelonephritis, and endocarditis (22 cases), and recent extensive myocardial infarctions (six cases). There was a single case of disseminated tuberculosis. This patient also showed caseating granulomas within the parathyroid gland, along with multiple perivascular lymphocytic infiltrates. This article's conclusions highlighted only one patient with true lymphocytic parathyroiditis in a patient with myocardial infarction, and proposed an autoimmune process.

The Thiele study showed 10 patients with secondary hyperparathyroidism, but no cases of primary hypoparathyroidism/hyperparathyroidism. It focused mostly on the problem of transition between diffuse and nodular hyperplasia and adenoma. The article described four patients with purulent destruction of parathyroid parenchyma in the setting of septicaemia or continuity from infected tracheostomies. It also described diffuse lymphocytic infiltrates in an unknown number of patients, but these findings were dismissed. The article concluded that no single case of true lymphocytic parathyroiditis was observed. The results of the autopsies studies are summarized in Table 2.

Table 3 gives clinical details of the 15 cases of parathyroiditis identified from the literature. All patients included had clear histological evidence of the disease, as described above. We reclassified three cases, described by the authors as lymphocytic infiltrate of the parathyroid gland, as histologically consistent with parathyroiditis. These patients were therefore reclassified as having parathyroiditis. Apart from the autopsy studies, all other patients showed parathyroid hyperfunction.

In surgical pathology material, only five case reports mentioned the presence of lymphocytic infiltrate of the parathyroid gland in patients with primary hyperparathyroidism. All patients (5, 100%) were found to have

a parathyroid adenoma (Table 4). Associated diseases were found in two of four (50%; one case had no data available). Associated diseases were far more common in the single autopsy cases (5/7, 71%) (Table 4). Table 6 shows that associated diseases were much more common in patients with simple lymphocytic infiltrate of the parathyroid gland (73.9%) than in patients with parathyroiditis (31.2%) (χ^2 11.1, $P = 0.001$). Granulomatous disease of the parathyroid gland is surprisingly rare. Only 11 cases have been identified, and the clinical details of these are outlined in Table 5.

The relative gene expression for each marker is shown in Figure 4. All markers for our case of hyperplastic parathyroiditis were in the range of hyperplastic-adenomatous lesions of the parathyroid gland, with the exception of *CD68*, which was significantly upregulated, reflecting the presence of histiocytic infiltrate [also supported by mannose 6-phosphate receptor (*M6PR*) upregulation]. Hypoxia-inducible factor 1A (*HIF1A*) and malate dehydrogenase 2 (*MDH2*) upregulation suggested an ischaemic background and a reactive mitochondrial process. The upregulated carbonic anhydrase 4 (*CA4*) expression is consistent with hyperparathyroidism.

Discussion

The term parathyroiditis has been used with some inconsistency. Some authors use it to describe any lymphocytic infiltrate in the parathyroid gland, whereas others employ it as a specific term for evidence of an immune process residing in the parathyroid gland.³⁶ Other authors use the term lymphocytic infiltrate of the parathyroid gland to characterize what other authors would have described as parathyroiditis.^{23–25} Because of this terminological variation and the paucity of recent studies, it is not generally clear how to classify inflammatory parathyroid entities.

We start from the general observation that any lymphocytic infiltrate defines a primary inflammatory condition of the involved organ. Genuine organ-related inflammation requires evidence of an organized immune process, e.g. in germinal centres, and/or evidence of immune-mediated cellular or interstitial damage. There are two fundamentally different patterns of distribution of immune cells in the parathyroid gland. The non-specific pattern is marked by perivascular lymphocytic infiltrates without evidence of lymphocyte maturation or immune-mediated tissue damage, such as fibrosis or epithelial degeneration. The pattern of lymphocytic parathyroiditis is defined by interstitial chronic inflammation with mature plasma cells and/or

Table 2. Lymphocytic infiltrates—large autopsy studies

Study	No. of autopsies	No. of glands removed	Cases with lymphocytic infiltrate, <i>n</i> (%)	Gender Male/female, <i>n</i>	Hypoparathyroidism/hyperparathyroidism	Associated diseases*, <i>n</i> (%)	No associated disease, <i>n</i> (%)
Seemann ¹⁰	225	NA	38 (16.9)	21/17	2 × sHPT 0 × hypoparathyroidism 0 × pHPT	28 (73.7)	10 (26.3)
Thiele ³⁶	589	1637	4 (0.7)	—	10 × sHPT 0 × hypoparathyroidism 0 × pHPT	4 (100.0)	0
Reiner ²⁴	144	190	15 (10.4)	7/8	0 × pHPT	12 (80.0)	3 (20.0)

NA, Not available; pHPT, primary hyperparathyroidism; sHPT, secondary hyperparathyroidism.

*Associated diseases; these include septicaemia, septic shock, myocardial infarction, and other generalized inflammatory conditions.

germinal centers, along with evidence of epithelial reaction (either degenerative or proliferative). Our reported case clearly documents these defining elements (Figures 2 and 3), along with molecular markers supporting a histiocytic component (*CD68* upregulation) in an ischaemic background (*HIF1A* upregulation) with mitochondrial reaction (*MDH2* upregulation) and hyperparathyroidism (*CA4* upregulation). In light of this definition, we have reviewed all published cases. Lymphocytic infiltrates are not uncommon, and have been identified in 6% of nearly 1000 autopsy cases in three large series of unselected patients (Tables 2 and 4). They do not seem to relate to functional hyperparathyroidism or hypoparathyroidism, and the autopsies have not identified organ damage related to parathyroid dysfunction. In contrast to this frequent presentation, genuine parathyroiditis is rare (only 15 cases, four of which were identified among 814 autopsy cases, accounting for a total of no more than 0.5%) (Tables 2–4). If the three cases reported in autopsy case reports are excluded from statistical analysis, the frequency drops to 0.1%. We can safely conclude that genuine parathyroiditis is a very rare condition, on the basis of both autopsy series and the low number of surgical specimens. These surgical specimens were obtained with the aim of curing primary and secondary hyperparathyroidism. We think that the association with parathyroid hyperfunction is spurious and is related to the sampling mechanisms, as parathyroid removal is almost always performed in the setting of hyperfunction.

We conclude that these two patterns are not only morphologically distinct but also pathogenetically different. Lymphocytic infiltrates of the parathyroid gland appear to be statistically associated with systemic

disease; this observation is significantly less common in parathyroiditis. We propose that the basis of this finding is directly related to the origin of the lymphocytic infiltrate. It is clearly associated with two conditions that would generally impact on venule integrity of the parathyroid gland, the neck, or beyond. Septicaemia and septic shock are characterized by a loss of integrity of the small vessels caused by bacterial toxins and excessive production of immune mediators by the human body. Depending on the degree of damage, the capillary leak progresses from simple oedema to massive loss of intravascular protein, lymphocytic extravasation, and finally microhaemorrhage into multiple organs.^{37,38} The other condition associated with perivenular diffuse lymphocytic infiltrates is myocardial infarction. Left heart failure leads to right heart failure, venous congestion, increased hydrostatic pressure, and secondary disruption of venule integrity, especially when reduced oxygen delivery enhances tissue vulnerability (Table 6).

The above concept provides significant help in understanding the more frequent non-specific pattern, but it does not shed any light on the origin of the primary parathyroid immune process. The nature of the current data does not invite any related speculations. Perhaps the most remarkable observation of this study is the rarity of specific inflammatory processes in the parathyroid gland. This is in striking contrast to the neighbouring endocrine organ, i.e. the thyroid, where autoimmune or perhaps infection-related thyroiditis is observed with a lifetime incidence of ~10%.^{2,5} For some reason, the parathyroid gland is either poorly antigenic or protected against the processes that initiate so-called autoimmunity. The latter observation could become relevant in the perspective of transplantation of small cell volumes.

Table 3. Parathyroiditis—clinical presentation

Patient (study)	Gender	Age (years)	pHPT	PTH		Surgery	Glands involved	Hyperplasia/adenoma	Other glands biopsied	Associated disease†	Size (mm)	Outcome
				Ca ²⁺ (mm)	(× upper limit of normal)*							
Present case	Male	42	sHPT	2.2	26.6	Thoracotomy	Ectopic	Hyperplasia	Yes (×4) (hyperplasia)	Yes	35	Cured
Kovacs ¹⁷	Female	43	Yes	2.6	Elevated	PTx	Right inferior	Adenoma	No	No	17	Cured
Fruto-Katos ¹⁵	Female	67	Yes	4.1	3.1	PTx	Left superior	Adenoma	No	No	NA	Persistent
Vaizey ¹⁹	Female	76	Yes	2.7	3.0	PTx	Left inferior	Hyperplasia	Right inferior (normal)	No	8	Persistent
Bonderson ¹²	Male	62	Yes	2.8	NA	PTx	Multiple (×3)	Hyperplasia	No	No	NA	Cured
Bonderson ¹²	Male	23	Yes	2.7	NA	PTx	Multiple (×3)	Hyperplasia	No	Yes	NA	Cured
Van-de ca ²⁰	Male	85	NA	NA	Hypo	Autopsy	NA	NA	–	Yes	NA	–
Boyce ¹³	Female	48	NA	NA	NA	Autopsy	NA	NA	–	No	NA	–
Italian ¹⁶	Male	63	Yes	3.0	NA	PTx	Single (orthotopic)	Hyperplasia	No	No	9	Persistent
Chetty ¹⁴	Male	57	Yes	3.4	1.4	PTx	Right + left inferior	Hyperplasia	No	No	20	Cured
Sinha ¹⁸	Male	35	Yes MEN	2.7	0.6	PTx	Right + left inferior + ½ left superior	Hyperplasia	No	No	15	Cured
Seemann ¹⁰	Male	63	NA	NA	NA	Autopsy	NA	NA	–	Yes	NA	–
Danisch† ²⁴	Male	66	NA	NA	NA	Autopsy	NA	NA	–	Yes	NA	–
Versse† ²⁵	Female	74	Yes	2.9	1.9	PTx	Single (orthotopic)	Adenoma	Yes (×1) normal	No	14	Cured
Versse† ²⁵	Female	42	Yes	2.9	2.2	PTx	Single (orthotopic)	Adenoma	Yes (×3) normal	No	5	NA
Lawton† ²³	Female	59	Yes	NA	NA	PTx	Right superior	Adenoma	Yes (×3) normal	No	35	NA

Hypo, hypoparathyroidism; MEN, Multiple Endocrine Neoplasia; NA, not available; pHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTx, parathyroidectomy; sHPT, secondary hyperparathyroidism.

*Times the upper normal limit of the method utilized.

†Associated conditions: these include septicaemia, septic shock, myocardial infarction, and other generalized inflammatory conditions.

‡These studies used the term lymphocytic infiltrate of the parathyroid gland to characterize what histologically looks like parathyroiditis.

Table 4. Lymphocytic infiltrate—clinical presentation from case reports

Patient (study)	Gender	Age (years)	PTH			Surgery	Glands involved	Hyperplasia/adenoma	Other glands biopsied	Associated diseases†	Size (mm)	Outcome
			pHPT	Ca ²⁺ (mm)	(× upper limit of normal)*							
Lam ²²	Female	70	Yes	3.2	3.0	PTx	Right superior	Adenoma	No	Yes	20	Cured
Fallone ²¹	Male	29	Yes	NA	5.8	Sternotomy	Ectopic	Adenoma	Yes (×4) (normal)	Yes	45	Cured
Lawton ²³	Female	68	Yes	2.6	NA	PTx	Left superior	Adenoma	Right + left superior (normal)	No	25	NA
Lawton ²³	Female	59	Yes	NA	NA	Tx and PTx	Single (orthotopic)	Adenoma		NA		
Lawton ²³	Male	60	Yes	2.6	NA	PTx	Left superior	Adenoma	Right superior (normal)	No	15	NA
Wirth ²⁴	Female	61	NA	NA	NA	Autopsy	Single	–	–	No	–	–
Haberfeld ²⁴	Female	31	NA	NA	NA	Autopsy	Multiple (×3)	–	–	Yes	–	–
Kraus ²⁴	Female	32	NA	NA	NA	Autopsy	Multiple (×2)	–	–	Yes	–	–
Guizetti ²⁴	Female	50	NA	NA	NA	Autopsy	Multiple (×4)	–	–	Yes	–	–
Guizetti ²⁴	Male	46	NA	NA	NA	Autopsy	Single	–	–	Yes	–	–
Koopman ²⁴	Male	70	NA	NA	NA	Autopsy	NA	–	–	Yes		
Groszer ²⁴	NA	45	NA	NA	NA	Autopsy	NA	–	–	No	–	–

NA, not available; pHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTx, parathyroidectomy; Tx, thyroidectomy.

*Times the upper normal limit of the method utilized.

†Associated conditions: these include septicaemia, septic shock, myocardial infarction, and other generalized inflammatory conditions.

Table 5. Granulomatous inflammation of the parathyroid

Patient (study)	Gender	Age (years)	PTH		Surgery	Glands involved	Hyperplasia/adenoma	Other glands biopsied	Associated disease†	Size (mm)	Outcome
			Ca ²⁺ (mmol/L)	($\times$ upper limit of normal)*							
Sarcoidosis ²⁶ (Balasan)	Female	70	Yes	3.5	Normal	PTx	Right inferior	Adenoma	No	NA	Persistent
Sarcoidosis ³⁵ (Taguchi)	Female	55	Yes	3.0	2.1	PTx	Left superior	Adenoma	Left inferior (granulomatous)	48.0	Cured
Sarcoidosis ³⁰ (Schweitzer)	Female	74	Yes	3.8	Elevated	PTx + LNs	Left superior	Adenoma	Three remaining (normal)	23.0	Cured
Sarcoidosis ³² (Robert)	Male	15	Yes	3.2	4.5	PTx + LNs	Multiple ($\times 4$) + LNs	Hyperplasia	–	NA	Cured
Sarcoidosis ³³ (Robinson)	Female	56	Yes	3.9	1.5	Neck exploration + thoracotomy	Ectopic	Adenoma	No	Yes	60.0 Cured
Sarcoidosis ³¹ (Chaychi)	Male	67	Yes	2.8	2.4	PTx	Right inferior + LNs	Adenoma	No	Yes	48.0 Cured
TB parathyroid ²⁷ (Kabbaj)	Female	49	sHPT	NA	Elevated		Adenoma	No	No	NA	NA
TB parathyroid ²⁸ (Kar)	Female	36	pHPT	3.2	36.4	en bloc + LN	Right inferior + LNs	Adenoma	No	30	NA
TB parathyroid ²⁹ (Sadideen)	Female	36	tHPT	2.7	12.5	en bloc + LN	Multiple ($\times 4$) + LNs	Hyperplasia	–	NA	NA
TB parathyroid ¹⁰ (Seemann)	NA	NA	No	NA	NA	Autopsy	–	–	?	NA	–
Granulomatous ¹¹ (Anaforoglu)	Female	50	pHPT	NA	1.6	PTx + LNs	Left inferior	Adenoma	No	20.0	Cured
Granulomatous ³⁴ (Iacob)	Female	35	pHPT	NA	Elevated	PTx	Right inferior	Adenoma	No	40.0	Cured

LN, Lymph node; NA, not available; pHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTx, parathyroidectomy; sHPT, secondary hyperparathyroidism; TB, tuberculous; tHPT, tertiary hyperparathyroidism.

*Times the upper normal limit of the method utilized.

†Associated conditions: these include septicaemia, septic shock, myocardial infarction, and other generalized inflammatory conditions.

Figure 4. Relative gene expression for each marker.

Table 6. Association of underlying diseases with lymphocytic infiltration and true parathyroiditis

Diagnosis	Patients, <i>n</i>	Associated disease, <i>n</i> (%)	No associated disease, <i>n</i> (%)	<i>P</i> -value
Lymphocytic infiltrates	69	51 (73.9)	17 (24.6)	<0.001
Parathyroiditis	16	5 (31.2)	11 (68.7)	

We also identified 14 cases of granulomatous inflammation of the parathyroid gland, including six cases of sarcoidosis, four cases of tuberculosis, and two non-specific granulomatous processes (Table 5). Again, the rarity of this association warrants attention when seen on the background of thousands or millions of described cases of granulomatous processes in other tissues.^{1,39,40}

We agree with Furuto-Kato¹⁵ that parathyroiditis may be associated with significant functional aberrations (Figure 1); an explanation of this observation is offered by molecular studies showing the impact of inflammatory substances on functional regulation of the parathyroid gland.^{41,42} Such immune mediators could plausibly be liberated and act as paracrine regulators in the vicinity, for example, of germinal centres of the parathyroid chief cell mass.

Conclusion

Genuine inflammatory disorders of the parathyroid gland are rare, and may result in functional dysregulation. The term parathyroiditis should be reserved for lesions with evidence of a primary parathyroid immune process. The common lymphocytic infiltrate is a non-organ-specific reflection of a capillary permeability change and, at best, indicates clinical disease. The

diagnosis of lymphocytic infiltrate as such should not lead to any other examinations or diagnostic procedures. The rarity of granulomatous disease in the parathyroid gland points to specific immunological properties of the parathyroid gland.

Disclosure statement

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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